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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,894	02/08/2002	Claude Negrier	06478.1465	8035

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EXAMINER
SCHNIZER, HOLLY G

ART UNIT	PAPER NUMBER
1653	8

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	10/067,894	NEGRIER ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5,6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

The Preliminary Amendment filed March 10, 2003 has been entered. Claim 4 has been cancelled. Claims 10-11 have been added. Therefore, Claims 1-3 and 5-11 are pending and have been considered in this Office Action.

Specification

The Specification is objected to because it contains Figures 1-4 but does not contain a Brief Description of the Drawings. Correction is required.

Claim Objections

Claim 11 is objected to because the claim refers to HEL cells. This cell line would be more accurately identified by its full name "human erythroleukemia" cells. This objection would be overcome by adding the full name of the cell line followed by its acronym as follows "human erythroleukemia (HEL)". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 10 is inoperable since hematopoietic cells are not platelets and since platelets do not have a nucleus required for transcription (which in turn is required for expression of the protein). Platelets are cytoplasmic fragments of megakaryocytes and do not contain a nucleus. DNA expression requires transcription of the DNA into mRNA and then translation of the mRNA into protein. Transcription occurs in the nucleus of a cell. Thus, it appears that platelets would not support expression of transfected DNA because platelets do not contain a nucleus. Therefore, there are no promoters that target expression of proteins to platelets. Perhaps the claim was intended to read "wherein said hematopoietic cells are megakaryocytes". Correction is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 5-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 and 5-11 are indefinite as to whether the claimed modified FVIII cDNA contains only an intron and a promoter or whether it is a factor VIII cDNA containing an inserted intron and a promoter. As written, the claim implies that the "modified" cDNA comprises only an intron (which is not a factor VIII intron; see line 3 of clm. 1) and a promoter. However, this is confusing since the

claim is drawn to a FVIII cDNA. This rejection could be overcome by deleting "modified" in lines 1 and 5 of claim 1 (for example) and deleting "wild-type" in line 3 of the claim. If this amendment is made then Applicant is reminded that any dependent claims should be reviewed and amended appropriately to maintain antecedent basis.

Claim 3 is unclear as to the identity of the intron. Is the intron one from a truncated Factor IX or is the intron itself truncated? Clarification is required.

Claim 10 is indefinite for the limitation "wherein said hematopoietic cells are platelets". Platelets are cytoplasmic fragments of megakaryocytes and do not contain a nucleus therefore platelets are not hematopoietic cells. Correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 5-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Connelly et al. (Human Gene Therapy (1996) 7: 183-195; referenced in IDS of Paper No. 6) and Negrier et al. (EP 1 048 726, 11-02-00; referenced in IDS of Paper No. 5), in view of and Uzan et al. (J. Biol. Chem. (1991) 266(14): 8932-8939; referenced in IDS of Paper No. 4), Hoeben et al. (Thrombosis and Haemostasis (1992) 67(3): 341-345; referenced in IDS of Paper No. 5), and Hao et al. (Human Gene Therapy (1995) 6: 873-880).

Connelly et al. and Negrier et al. show that it was well known in the art at the time of the invention that insertion of the Factor IX intron 1 into a B-domain deleted factor VIII cDNA resulted in increased expression of factor VIII. Connelly et al. teach that placement of the first intron of the human Apo A1 gene at the ATG of the FVIII coding region in a factor VIII cDNA (see p. 186, Col. 1, 2nd paragraph) results in increased expression of functional FVIII in mice that were administered a viral vector containing the cDNA. Negrier et al. teach the insertion of a factor IX truncated intron I into several locations of the FVIII cDNA (see p. 4, last section). Negrier et al. show that the FVIII I1 +13 mRNA was expressed in larger amounts and led to about a 9 times protein increase (see p. 6, lines 53-58 and Figs. 5-7).

Neither Connelly et al. nor Negrier et al. teach using a promoter which targets expression of the factor VIII cDNA to hematopoietic cells.

Uzan et al. provides a characterization of the GPIIb promoter and concludes that the GPIIb promoter contains sufficient information to direct high level tissue specific expression and suggests that this promoter can be used to target expression of heterologous genes in megakaryocytes (hematopoietic cells; see p. 8932, 1st paragraph of intro. And p. 8938, Col. 2, last two lines). Uzan et al. transfects HEL cells with a vector containing a CAT gene under the control of the GPIIb promoter in order to test the promoter. A search of the prior art appears to indicate that the GPIIb promoter was the only available hematopoietic specific promoter that was fully characterized at the time of the invention.

Hoeben et al. teach that the haematopoietic system is particularly attractive for gene therapy of bleeding disorders because the technology to manipulate and transplant bone marrow is available, the presence of haematopoietic stem cells in bone marrow offers the possibility to achieve persistent presence of genetically modified blood cells in patients, and since the haematopoietic system would secrete the protein directly into the systemic circulation (see p. 341, Col. 2, 2nd full paragraph). Hoeben et al. report the infection of murine bone marrow cells with a recombinant retrovirus encoding FVIII and the transplantation of the infected bone marrow into lethally irradiated mice. Hoeben et al. were not able to show expression either at the RNA level or at the protein level and conclude that low expression might be due to irreversible inactivation of the viral long terminal repeat promoter/enhancer (p. 344, Col. 1,

1st full paragraph of main text). Hoeben et al. state that use of vectors in which factor VIII is driven by either the Herpes Simplex Virus Thymidine kinase gene promoter or the Simian Virus 40 (SV 40) promoter resulted in undetectable quantities of factor VIII secretion in infected murine fibroblast cell lines (p. 344, Col. 2, 2nd paragraph).

Hao et al. teach that because the normal site of factor IX synthesis is in hepatocytes, initial attempts to express factor IX focused on hepatocyte transduction. However, Hao et al. points out that clinical protocols to achieve stable transduction in hepatocytes are cumbersome since they require partial hepatectomy to isolate hepatocytes followed by intrasplenic or portal vein administration. And, Hao et al. suggests using hematopoietic stem cells as an alternative because they are easier to manipulate and transduce, they have the potential to provide continuous, persistent blood factor replacement and are more readily obtained than hepatocytes (see p. 878, paragraph bridging Col. 1-2). Hao et al. states that the question of using hematopoietic cells for expression of factor IX is whether the cells can process and secrete sufficient amounts of biologically active factor IX to prevent or reduce excessive bleeding (p. 874, 2nd paragraph). Thus, Hao et al. show the successful expression of biologically active factor IX induced by PMA in HL-60 cells (a hematopoietic cell line). Hao et al. also suggests using hematopoietic specific promoters (p. 879, Col. 1, lines 27-28).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the factor VIII cDNA taught in Connelly et al. and Negrier et al. such that it was replaced the FIX sequence in the vector taught

in Hao et al. and such that it contained the hematopoietic specific promoter, GPIIb characterized in Uzan et al. It would have also been obvious to one of ordinary skill in the art at the time of the invention to use the DNA construct in a method of making factor VIII as taught in Connelly et al., and Negrier and Hao et al.

Both Hoeben et al. and Hao et al. teach the benefits of developing a gene therapy strategy to express blood factors in hematopoietic cells for treatment of hemophilia. Hoeben et al. teaches that the failure in the attempt at *in vivo* expression of factor VIII in hematopoietic cells is due to inactivation of the promoter and that strategies will have to be made to overcome this problem (see p. 344, Col. 2, 2nd paragraph). One of ordinary skill would have recognized that a logical strategy would be to work out the system of expression in hematopoietic cell lines to find vectors that would provide the high levels of expression of FVIII as was done successfully in Hao et al. for factor IX. Since Hao et al. reports successful expression of factor IX in hematopoietic cell lines, one of ordinary skill in the art, trying to improve the expression strategy of Hoeben et al., would have been motivated to use the vector of Hao et al. to express high levels of factor VIII in hematopoietic cells. One of ordinary skill would have been motivated to use the FVIII cDNAs containing introns as taught in Connelly et al. and Negrier et al. in the vectors taught in Hao et al. because Connelly et al. and Negrier et al. teach that the cDNAs described therein produce high levels of FVIII. In addition, Hoeben et al. suggest that the problem of expression in their system was due to inactivation of the retroviral promoter by the hematopoietic cells. Hoeben et al.

also states that other viral promoters had not worked (p. 344, Col. 2, 2nd paragraph). Thus, one of ordinary skill would have been motivated to use a hematopoietic specific promoter, as suggested by Hao et al. in order to overcome this problem. One of ordinary skill would have had a reasonable expectation of success in using the GPIIb promoter characterized in Uzan et al. since Uzan et al. shows that this promoter directs high level specific expression in megakaryocytic cells. Thus, it appears that the claims are unpatentable over the prior art of record.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Connelly et al. ,Negrier et al., Uzan et al., Hoeben et al., and Hao et al. as applied to claims 1-3 and 5-9 above, and further in view of Greenberg et al. (Blood (1988) Vol. 72, No. 6, pp. 1968-1977; referenced in IDS of Paper No 4).

The teachings of Connelly et al. ,Negrier et al., Uzan et al., Hoeben et al., and Hao et al. have been described above. The above references do not teach using the Dami cell line in methods of producing Factor VIII.

Greenberg et al. teaches that PMA increases expression of GPIIb expression in Dami cells (see abstract).

Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to use Dami cells in a method of producing factor VIII using a construct containing a factor VIII cDNA with an inserted intron and a GPIIb promoter as suggested in the combined teachings of Connelly et al., Negrier et al., Uzan et al., Hoeben et al., and Hao et al. since Dami cells, like HL-60 cells

used in Hao et al. or HEL cells used in Uzan et al, allow for induction of high levels of expression from the GPIIb promoter using PMA. Moreover, one of ordinary skill, trying to optimize expression of FVIII for future use in gene therapy, would have been motivated to use Dami cells since Greenberg et al. states that they resemble normal human megakaryocytes more closely than previously reported cell lines (see p. 1976, Col. 1, 2nd paragraph).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 11 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 13 of copending Application No. 09/559,344. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claims 13 of the '344 application differs from Claim 11 of the instant application in that it fails to disclose the specific cell lines used in the methods. However, the '344 application teaches that human erythroleukemia cell line that has megakaryocytic markers can be used in the method (p. 2)and describes the successful use of HEL cells in the expression of factor IX. Therefore, it would have been obvious to choose HEL cells as the specific cell line to use in the method of claim 13 of the '344 application. One of ordinary skill would have been motivated to use the HEL cells in the method since they had already been used successfully.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-3, 5-9 and 11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 09/559,344 in view of Connelly et al. (Human Gene Therapy (1996) 7: 183-195; submitted in IDS of Paper No. 6) and Negrier (EP 1 048 726, 11-2-00; submitted in IDS of Paper No. 5).

The DNA construct and methods of Claims 1, 2, 6, and 8-11 of the '344 application differ from Claims 1-3 and 5-9 of the instant application in that they fail to disclose that the DNA encoding the blood coagulation factor is a FVIII cDNA having inserted therein a factor IX truncated intron 1 or having inserted therein an intron at the positions of intron 1 and 13. However, both Connelly et al. and Negrier et al. teach that insertion of introns into factor VIII cDNA results in

increased expression of factor VIII and Negrier et al. teach that a factor VIII cDNA with factor IX intron 1 inserted into the positions of intron 1 and intron 13 of factor VIII has increased expression than the original factor VIII cDNA (see figs. 5-7). Therefore, it would have been obvious modify the method of claim 1 of the '344 application such that the DNA encoding the blood coagulation factor was a factor VIII cDNA containing factor IX introns at positions 1 and 13 of the factor VIII sequence. One having ordinary skill in the art would have been motivated to select such a coagulation factor sequence to optimize the production of factor VIII for use in treatment of hemophilia.

This is a provisional obviousness-type double patenting rejection.

Claims 1-3, 5-9 and 11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 7 of copending Application No. 09/880,887 in view of Hao et al. (Human Gene Therapy (1995) 6: 873-880), Hoeben et al. (Thromb. Haemost. (1992) 67(3): 341-345), and Uzan et al. (J. Biol. Chem. (1991) 266(14) 8932-8939).

The method and DNA construct used in the method of Claim 7 differs Claims 1-3, 5-9, and 11 of the instant application in that it fails to disclose that the promoter is the hematopoietic specific promoter, GPIIb. However, Hao et al. and Hoeben et al. teach the benefits of expression of factors VIII and IX in hematopoietic cells and Uzan et al. shows that the GPIIb promoter directs high level of specific expression in HEL cells. Thus, it would have been obvious to

modify the method of claim 7 of the '887 application such that the DNA used to express factor VIII contained the GPIIb promoter. One having ordinary skill would have been motivated to use the GPIIb promoter since Hao et al. suggests using hematopoietic specific promoters (p. 879, Col. 1, lines 27-28) to improve the system taught therein.

Claims 1-3, 5-9 and 11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, and 5 of U.S. Patent No. 6,271,025 in view of Hao et al. (Human Gene Therapy (1995) 6: 873-880), Hoeben et al. (Thromb. Haemost. (1992) 67(3): 341-345), and Uzan et al. (J. Biol. Chem. (1991) 266(14) 8932-8939).

Claims 1, 3, and 5 of the patent differ from Claims 1-3, 5-9, and 11 of the instant application in that they do not disclose a promoter that is a hematopoietic specific promoter, GPIIb. However, Hao et al. and Hoeben et al. teach the benefits of expression of factors VIII and IX in hematopoietic cells and Uzan et al. shows that the GPIIb promoter directs high level of specific expression in HEL cells. Thus, it would have been obvious to modify the cDNA of claims, 1, 3, and 5 of the patent to contain the GPIIb promoter. One having ordinary skill would have been motivated to use the GPIIb promoter with the factor VIII cDNA taught in the patent since Hao et al. teaches the benefits of expressing a related blood coagulation factor in hematopoietic cells and suggests using hematopoietic specific promoters (p. 879, Col. 1, lines 27-28) to improve the system taught therein.

Conclusion

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Christopher S. F. Low

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Holly Schnizer
March 26, 2003